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Changes in Anterior and Posterior Hippocampus Differentially Predict Item-Space, Item-Time, and Item-Item Memory Improvement

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Abstract

Relational memory requires the hippocampus, but whether distinct hippocampal mechanisms along the anterior-posterior axis are required for different types of relations is debated. We investigated the contribution of structural changes in hippocampal head, body, and tail subregions to the capacity to remember item-space, item-time, and item-item relations. Memory for each relation and volumes of hippocampal subregions were assessed longitudinally in 171 participants across 3 time points (M_{age} at T1= 9.45 years; M_{age} at T2= 10.86 years, M_{age} at T3= 12.12 years; comprising 393 behavioral assessments and 362 structural scans). Among older children, volumetric growth in: (a) head and body predicted improvements in item-time memory, (b) head predicted improvements in item-item memory; and (c) right tail predicted improvements in item-space memory. The present research establishes that volumetric changes in hippocampal subregions differentially predict changes in different aspects of relational memory, underscoring a division of labor along the hippocampal anterior-posterior axis.

Without the ability to retain relational information about life events our memories would be fragmentary, difficult to retrieve, and ultimately of little value. Relational memory depends on mechanisms that bind features of experiences into integrated event representations [1]; these features include where an event happened (item-space)[2], when it happened (item-time)[3], and with what other events it co-occurred (item-item)[4]. The hippocampus is critical for learning and recalling these arbitrary memory relations [5,6], but whether all types of memory relations are supported by the same or different hippocampal mechanisms is debated [7–9].

On the one hand, there is substantial evidence that the hippocampus is necessary to learn all arbitrary relations. For example, Konkel and colleagues found that adults with hippocampal lesions were equally impaired in their ability to remember spatial, temporal, or item-item relations [6]. On the other hand, at least some degree of segregation within the hippocampus has been reported [10]. Item-item relations may be supported by more anterior regions [11], whereas item-space relations may be supported more strongly by right-lateralized posterior hippocampal regions [12]. Here, we adopt a developmental approach to address the question of whether developmental improvements in these three forms of relational memory rely on structural changes in the hippocampus and, if so, whether they depend on the same or different subregions.

Recent research has highlighted age-related differences in hippocampal structure and function in children and adolescents and evidence of cross-sectional associations between volume and memory [13–16]. However, longitudinal evidence linking changes in hippocampal structure to memory development is lacking. We shed new light on these issues by capitalizing on a longitudinal design in which we assessed both structural changes in hippocampal head, body, and tail subregions and behavioral changes in an experimental task assessing item-space, item-time and item-item memory.

There are at least two lines of evidence suggesting that this approach may be particularly informative. First, initial cross-sectional findings suggested heterogeneous development of the hippocampus along the anterior-posterior axis with distinct relations with memory[14,16–18]. Second, heterogeneities in age-related differences in memory for spatial, temporal and associative information have been documented in cross-sectional studies against a backdrop of general memory improvement during childhood [15,19–21]. This body of research indicates that memory for spatial relations may be more robust at a younger age compared to memory for temporal relations [20–22] and item-item associative relations [22]. Overall, these two lines of evidence suggest a co-occurrence of distinct structural changes in the anterior and posterior hippocampus and distinct behavioral changes in relational memory, consistent with a functional segregation in the hippocampus during development. However, an important limitation of these cross-sectional studies is that it was not possible to examine whether developmental changes in hippocampal structures predicted developmental improvements in memory over time within the same individuals.

In the present study, we used a combination of experimental and longitudinal approaches to examine a cohort of 172 children between 7 and 15 years of age who underwent structural magnetic resonance imaging (MRI) and relational memory assessment on up to three measurement occasions (T1, T2, T3) (Fig. 1A; 362 longitudinal scans; 393 longitudinal behavioral assessments). The advantage of a longitudinal approach combining behavior and brain assessment is its potential to reveal how structural changes predict behavioral development, accounting for concurrent associations. Participants encoded triplets of novel visual objects, each appearing one at a time in one of three locations on the screen (Figure 1B, Top). Memory was tested immediately after study with a probe signaling whether participants were required to

retrieve item-space, item-time, or item-item associations (Figure 1B, Bottom).

The central hypothesis guiding the present research is that changes in hippocampal structure contribute to developmental improvements in relational memory. Specifically, we predicted that relational memory developed differentially as a function of type of relation, with the ability to remember item-space relations developing earlier than the other relations. We also predicted distinct developmental trajectories of hippocampal volume as a function of subregion, with the hippocampal head decreasing and the hippocampal body increasing in volume at least prior to age 10 [15]. Finally, we hypothesized that volumetric changes in hippocampal subregions would predict behavioral changes differently as a function of type of relation. For example, changes in more posterior subregions (i.e., tail) were expected to relate to the development of memory for item-space relations [10].

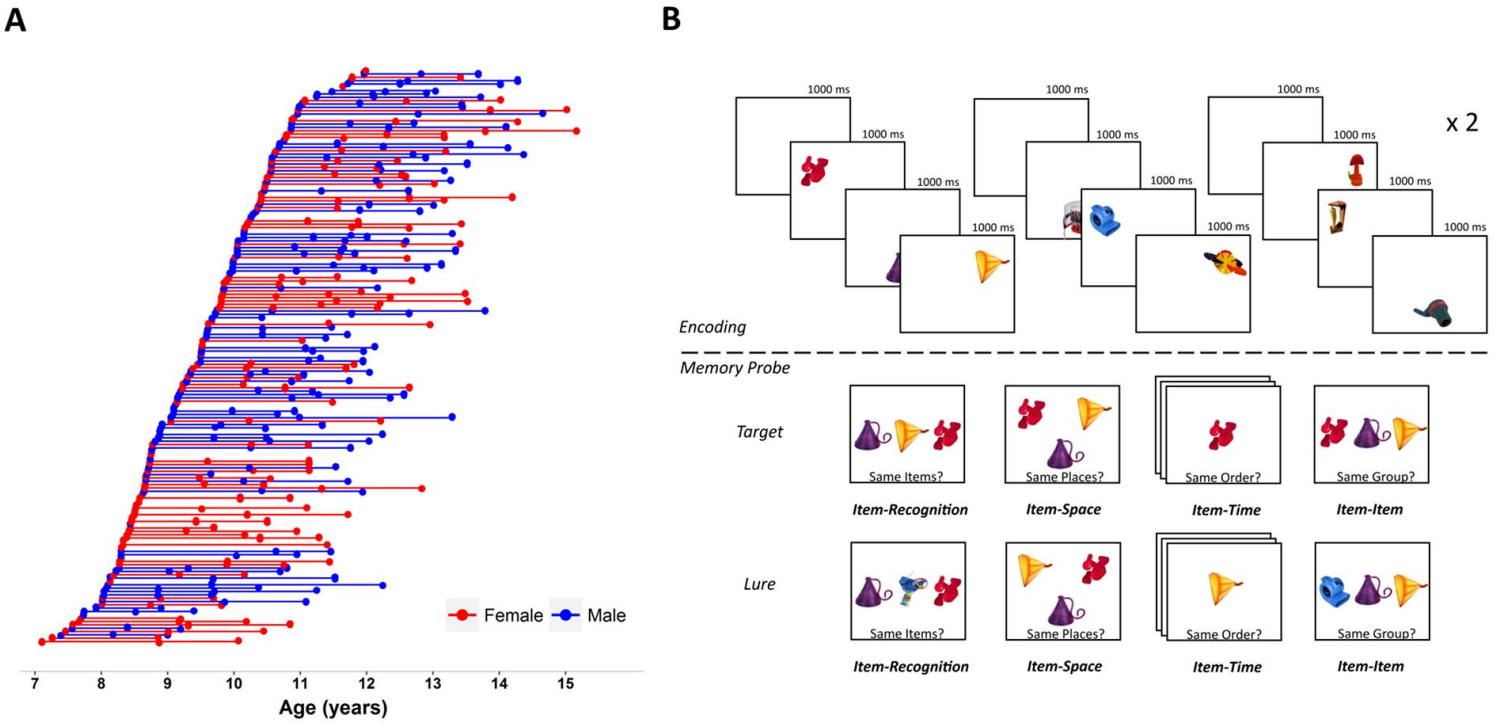

Figure 1. A. Longitudinal cohort of 172 children providing MRI structural images and relational memory assessments on up to three occasions (362 longitudinal scans, 393 longitudinal behavioral assessments). **B.** Triplet Binding Task (TBT). Encoding: Item-Recognition, Item-Space, Item-Time, and Item-Item relation conditions shared identical encoding procedures. Memory probe: Target and lure test trials for item-recognition, item-space, item-time, and item-item relation conditions, from left to right, respectively.

To briefly summarize our key and novel findings, we report that memory for item-space relations matured earlier than memory for item-time and item-item relations, and that the hippocampal head declined in volume throughout most of middle childhood, whereas hippocampal body increased in volume until approximately age 10 before declining. Finally, we report that volumetric increases in head and body predicted better item-time and item-time memory, whereas increases in tail volume predicted better item-space memory.

Results

We conducted longitudinal analyses using mixed effect models [23]. Memory for each relation was calculated as the difference between hit and false-alarm rates. Total hippocampal volumes were first extracted using the semi-automated procedure described in the Methods section, and were then manually segmented into head, body and tail based on established guidelines [14]. This segmentation had excellent inter-rater reliability (Head/Body Division: ICC=.98; Body/Tail Division: ICC=.99). Volumes were adjusted for intracranial volume (ICV) using regression methods [24]. In all models, the effect of age was separated into a time-varying within-subject effect (i.e., change in age since T1) and a time-invariant between-subject effect (i.e., age at T1) (25, 27; see Methods). In brain–behavior models, the effects of head, body, and tail volumes were similarly separated into a time-varying within-subject effect (i.e., changes in volume since T1) and a time-invariant between-subject effect (i.e., volume at T1).

In each longitudinal analysis, model comparisons were conducted to test whether the inclusion of key variables of interest increased model fit over baseline models, beginning with testing for main effects, and then systematically adding higher order interaction effects with these key variables. The full longitudinal models are described in Table 1. The key variables of interest in the behavioral models included the effect of age at T1 and change in age, as well as

the two-way interactions between these variables and three-way interactions with type of memory relation. The key variables of interest in the hippocampal models were also age at T1 and change in age, as well as their interaction, and three-way interactions with hippocampal subregion. Finally, in the brain–behavior models, the key variables of interest were volume of head, body, and tail at T1 and changes in these volumes since T1, as well as their interactions with age at T1 and change in age.

Table 1. Fixed and Random Effect Models

Behavioral: Memory = Sex + Item-recognition$_{T1}$ + Age$_{T1}$ * ΔAge * Relation + (1 + ΔAge | Participant)
Hippocampal: Volume = Sex + Hemisphere + Age$_{T1}$ * ΔAge * Subregion + (1 + ΔAge | Participant)
Brain–Behavior: Memory = Sex + Item-recognition$_{T1}$ + Head$_{T1}$ + Body$_{T1}$ + Tail$_{T1}$ + Age$_{T1}$* ΔAge * ΔHead + Age$_{T1}$ * ΔAge * ΔBody +Age$_{T1}$ * ΔAge * ΔTail + (1 + ΔAge | Participant)

Note: '*' denotes inclusion of main and interactive effects between operands. '(1 + Δ Age | Subject)' indicates a random intercept and slope model. Female gender, item-item relations, and hippocampal head served as reference categories. Brain-Behavior models examined each relation separately. T1 subscript denotes value at Time 1.

Distinct Developmental Trajectories of Relational Memory

We first conducted the longitudinal analysis of relational memory (See Table 1). Overall, relational memory was greater in children who were older at T1 ($\chi2$ = 17.8, *df* = 1, *p* <.0001; β=.18, *b* = .04, *t*(170) = 4.4, *p* <.0001), capturing cross-sectional differences, and it increased more as more time passed, as indicated by a positive association with change in age ($\chi2$ = 25.5 *df* = 1, *p* <.0001; β=.17, b=.04, *t*(121)=5.19, *p* <.0001). Improvements in relational memory over time were greater for children who were younger at T1 (age at T1 x change in age in years interaction; $\chi2$ = 7.90, *df* = 1, *p* = .005; β=.18, b=-.02, *t*(140)=-2.88, *p* = .004). We also found a significant effect of type of relation ($\chi2$ = 368.5, *df* = 2, *p* <.0001), such that the highest performance was observed for item-space memory (M=.45; SE= .01), which was greater than item-time (M=.36, SE=.01; *t* (864) = 7.1, *p* <.0001). Item-time was, in turn, greater than item-

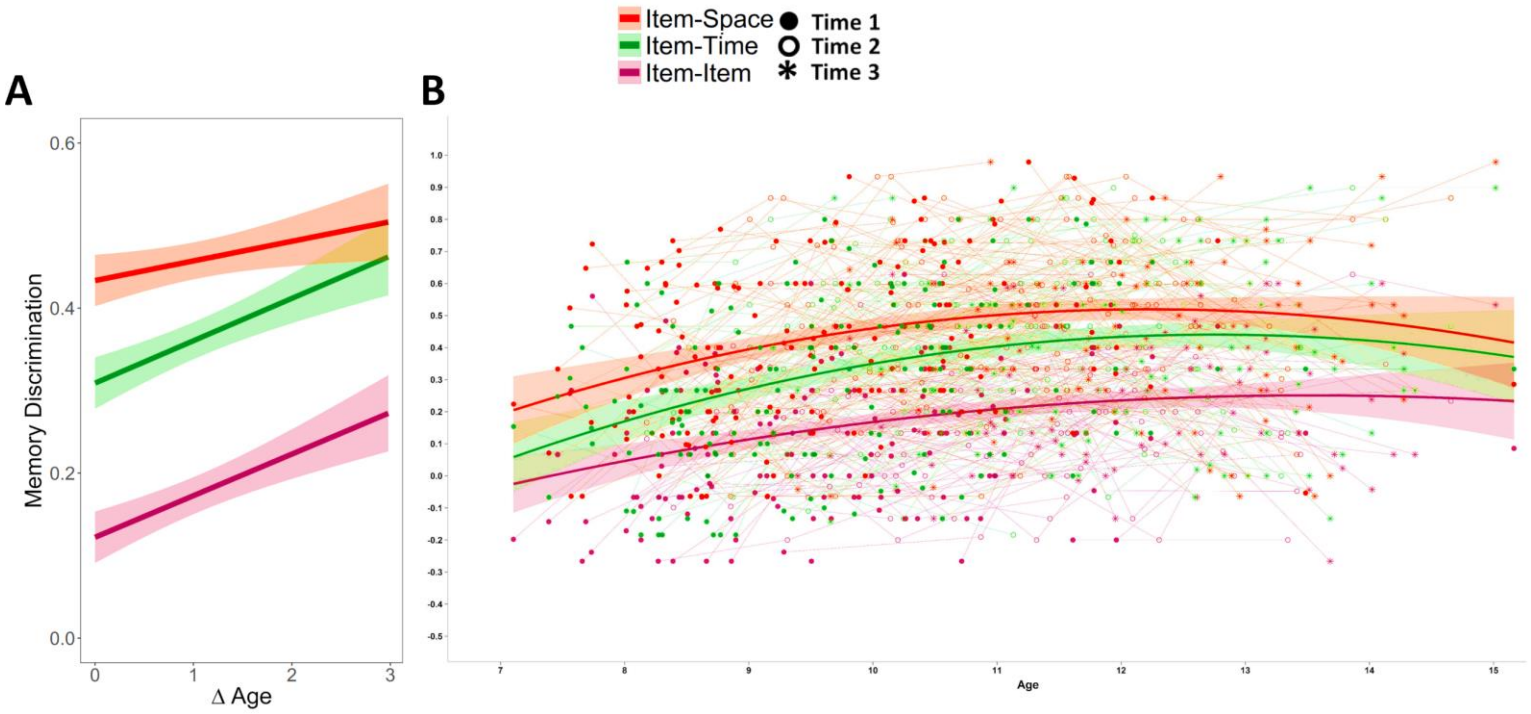

Figure 2. Developmental changes in memory for item-space, item-time, and item-item relations. Error bands represent 95% confidence intervals. **A.** Depicting the three-way interaction between memory relation, within-subject changes in age since Time 1 (ΔAge), and cross-sectional differences in the starting age at Time 1 (here at 8- and 11-years of age). **B.** A descriptive spaghetti plot of item-space, item-time, and item-item memory performance by years in age, with quadratic lines fitted. Note that the use of age conflates between-person cross-sectional differences with within-person changes, and thus these fit lines do not reflect true longitudinal change.

item memory (M=.17, SE .01; t (864) = 10.03, $p < .0001$). Consistent with our primary hypothesis, the magnitude of memory improvement over time depended on the type of relation, as indicated by a significant interaction between change in age and type of relation ($\chi 2 = 6.21$ $df = 2$, $p = .04$) (Figure 2). See Table 2 for parameter estimates for each type of relation separately, and Table S1 for parameter estimates testing the interaction with type of relation. The positive association between change in age and change in memory was stronger for item-time and item-item than for item-space (item-space: β=.09, $b = .02$, t (374) = 2.17, $p = .03$; item-time relative to

item-space, β=.08, *b* = .03, *t* (867) = 2.18, *p* = .03; item-item relative to item-space, β=.08, *b* = .03, *t* (867) = 2.11, *p* = .04). Associations between change in age and performance did not differ between item-time and item-item relations (*p* =.94). Model parameters predicted that item-space memory plateaued around 10.4 years, item-time memory around 12.2 years of age, and item-item around 12.5 years. Thus, consistent with prior work, item-space memory matured earlier than both item-item and item-time relations.

Table 2. Parameter Estimates for Item-Time, Item-Item and Item-Space Models

Effect	**Beta**	**b**	***SE***	***t***	***p***
Item-Time					
(Intercept)	–	.323	.023	14.3	<.001
Item-Recognition	.310	.353	.066	5.39	<.001
Male	-.048	-.025	.029	-.861	.390
Start-Age	.213	.044	.013	3.29	.001
ΔAge	.212	.051	.011	4.61	<.001
Start-Age x ΔAge	-.125	-.019	.009	-2.05	.043
Item-Item					
(Intercept)	–	.133	.019	6.93	<.001
Item-Recognition	.162	.151	.053	2.87	.005
Male	-.033	-.014	.023	-.605	.546
Start-Age	.204	.035	.012	2.95	.004
ΔAge	.244	.048	.009	5.27	<.001
Start-Age x ΔAge	-.128	-.016	.008	-2.07	.041
Item-Space					
(Intercept)	–	.457	.023	20.2	<.001
Item-Recognition	.328	.357	.065	5.49	<.001
Male	-.076	-.038	.029	-1.31	.191
Start-Age	.180	.036	.014	2.66	.009
ΔAge	.083	.019	.011	1.73	.086
Start-Age x ΔAge	-.139	-.020	.009	-2.18	.031

Notes: Model Fits: Item-Time: $\chi2 = 68.7$, $df = 5$, $p < 1.85e\text{-}13$; Item-Space: $\chi2 = 48.2$, $df=5$, $p = 3.3e\text{-}9$; Item-Item: $\chi2 = 48.0$, $df=5$, $p = 3.6e\text{-}9$; Interactions with sex were not significant ($\chi2s \leq 4.66$, $dfs=3$, $ps \geq .20$). Note: ΔAge is defined at time in years since Time 1. Item-recognition and Start-Age are centered at the mean at Time 1. Left hemisphere and female are reference categories.

159 **Distinct Developmental Trajectories of Hippocampal Subregions**

160 We assessed developmental changes in hippocampal head, body, and tail (See Table 1).
161 We found a significant interaction between change in age and hippocampal subregion ($\chi 2 = 8.83$
162 $df = 2$, $p = .012$), which was further moderated by age at T1 ($\chi 2 = 9.80$, $df = 3$, $p = .020$). As
163 predicted, we found distinct within-subject trajectories for the three subregions (Figure 3). See
164 Table S2 for parameter estimates of this full model. For completion, we also estimated
165 longitudinal models using total hippocampal volume, the results of which are reported in Table
166 S3. Given the differences in volumetric change as a function of subregion, we examined the
167 trajectory of each subregion separately.

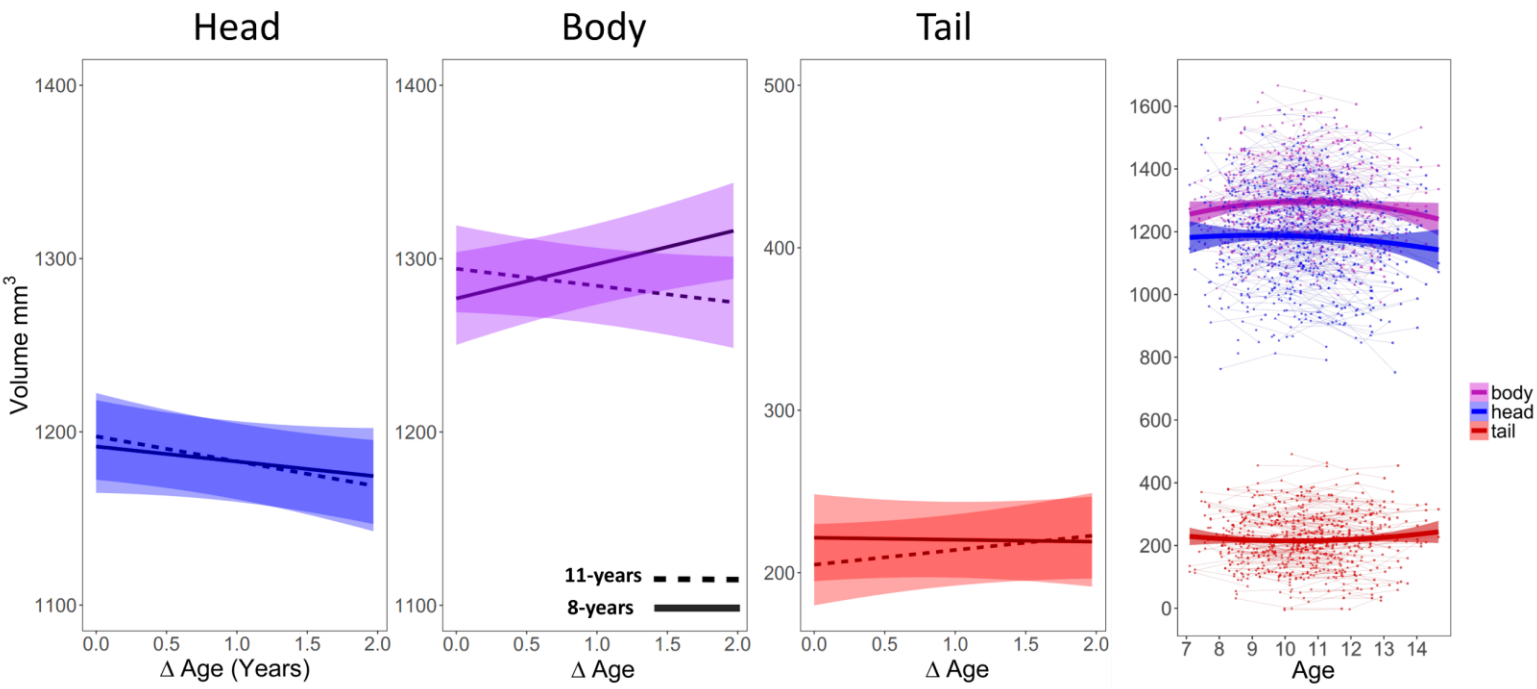

Figure 3. Developmental changes in head, body, and tail ICV-corrected volume. Error bands represent 95% confidence intervals. **A.** Depicting the three-way interaction between hippocampal sub-region, within-subject change in age since Time 1 (ΔAge), and cross-sectional differences in the starting age at Time 1 at 8- and 11-years of age. **B.** Spaghetti plots of head, body, and tail ICV-corrected volume over time with quadratic lines fitted.

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Table 3. Parameter Estimates for Models of Hippocampal Head, Body, and Tail Change

Sub-Region	Effect	Beta	b	*SE*	*t*	*p*
Head	(Intercept)	–	1128	16.4	68.8	<.001
	Male	.030	11.7	22.3	.525	.600
	Hemisphere [Right]	.313	106	5.23	20.2	<.001
	Start-Age (Mean-Centered)	.011	3.02	10.2	.298	.770
	ΔAge	-.060	-7.07	2.70	-2.62	.009
	Start-Age x ΔAge	-.056	-5.51	2.56	-2.16	.033
Body	(Intercept)	–	1314	13.4	98.1	<.001
	Male	-.133	-26.1	18.1	-1.44	.150
	Hemisphere [Right]	-.104	-33.5	4.93	-6.80	<.001
	Start-Age (Mean-Centered)	.015	1.40	8.35	.167	.873
	ΔAge	.012	1.68	2.53	.661	.514
	Start-Age x ΔAge	-.061	-4.86	2.39	-2.03	.042
Tail	(Intercept)	–	208	9.38	22.1	<.001
	Male	.067	11.5	12.6	.912	.363
	Hemisphere [Right]	.024	4.10	2.92	1.40	.164
	Start-Age (Mean-Centered)	-.042	-3.30	5.86	-.564	.572
	ΔAge	.022	1.76	1.50	1.17	.240
	Start-Age x ΔAge	.010	.538	1.42	.377	.712

Model Fits: Hippocampal Head: $\chi2 = 312$, $df = 5$, $p < 2.2e\text{-}1$; Hippocampal Body: $\chi2 = 51.4$, $df=5$, $p = 7.2e\text{-}10$; Hippocampal Tail: $\chi2 = 4.44$, $df= 5$, $p = .49$. Note: ΔAge is defined as time in years since Time 1; Left hemisphere and female are reference categories; Volumes are in cubic mm.

Hippocampal Head. As predicted, hippocampal head volumes declined over time, as indicated by the negative effect of change in age ($\chi2 = 5.63$, $df = 1$, $p = .02$; $b = -7.07$, t (449) = -2.62, $p = 9.2e\text{-}3$). This effect was moderated by age at T1 ($\chi2 = 4.65$, $df = 1$, $p = .03$; $\beta=-.06$, $b = -5.51$, t (457) = -2.16, $p = .03$), such that greater volumetric declines were observed in children the older you were at T1. Associations with change in age did not significantly differ between hemispheres ($\chi2 = .60$, $df = 1$, $p = .44$) or sex ($\chi2 = 2.58$, $df = 1$, $p = .11$) (Table 3). A descriptive examination of the partial derivatives of model parameters suggests that peak volume of hippocampal head occurred at 8.17 years of age before declining during late childhood.

Hippocampal Body. As predicted, hippocampal body exhibited a non-linear trajectory. Change in age significantly interacted with age at T1 ($\chi2 = 4.10$, $df = 1$, $p = .04$; β=-.06, $b = -4.86$, t (496) = -2.03, $p = .04$): The volume of the hippocampal body increased over time for younger children, but it declined for older children. Association with changes in age did not significantly differ by hemisphere ($\chi2 = .60$, $df = 1$, $p = .44$) or sex ($\chi2 = 3.4e\text{-}3$, $df = 1$, $p = .95$) (Table 3). A descriptive examination of the partial derivatives of model parameters suggests that peak volume of hippocampal body occurred at 9.79 years before declining in late childhood.

Hippocampal Tail. No significant developmental changes were observed for either left or right tail (Table 3).

Linking Hippocampal and Relational Memory Development

We examined whether and how volumetric changes along the anterior-posterior axis predicted the development of each type of memory relation (See Table 1). All models included volume at T1, changes in volume since T1, age at T1, and changes in age since T1, as well as their interactions. Volume and volume changes were in cubic millimeters for unstandardized betas. The primary longitudinal effects of interest were the two- and three-way interactions between age at T1, change in age, and change in volume. These interactions allow us to link developmental changes in volume to behavioral development, with the additional consideration that longitudinal relations may depend on the age at the start of the study. We started by examining item-time and item-item memory, because they showed the most robust behavioral change, and ended with item-space memory, which we established develops relatively earlier (see Methods for detailed description of the models). For these, left and right hippocampal volumes were summed because no hemispheric differences were observed.

Item-Time. Consistent with predictions, changes in hippocampal head, body, and tail predicted item-time memory. Specifically, we observed a significant three-way interaction between change in hippocampal subregion volumes, age at T1 and change in age ($\chi 2 = 12.1$, $df = 3$, $p = .007$) (See Table 4). Increase in head and body volumes, but not tail, significantly predicted greater memory performance after longer delays (e.g., a 3-year change is depicted in Figure 4A), but not shorter delays (e.g., a 1-year change in age is depicted in Figure S1A), indicating that several years were necessary for these brain-behavior relations to manifest. Furthermore, this result depended on age at T1. When the model was evaluated for children who

Table 4. Hippocampal Volume Predicting the Development of Item-Time Memory.

	Left and Right Hippocampal Sum				
Effect	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	-	3.2e-1	2.5e-2	13	<.0001
Item-Recognition	0.28	3.2e-1	7.4e-2	4.4	<.0001
Sex [Male]	-0.053	-2.8e-2	3.2e-2	-0.86	0.39
Start-Volume Head	-0.049	-4.5e-5	5.6e-5	-0.79	0.43
Start-Volume Body	-0.065	-7.0e-5	6.6e-5	-1.1	0.29
Start-Volume Tail	0.062	9.8e-5	9.9e-5	0.99	0.32
Start-Age	0.25	5.8e-2	1.7e-2	3.4	0.001
ΔAge	0.26	6.2e-2	1.3e-2	4.7	<.0001
ΔHead	-0.063	-1.9e-4	4.1e-4	-0.47	0.64
ΔBody	-0.056	-1.6e-4	3.8e-4	-0.43	0.67
ΔTail	-0.2	-1.4e-3	9.5e-4	-1.5	0.14
Start-Age x ΔAge	-0.13	-2.1e-2	1.2e-2	-1.7	0.095
Start-Age x ΔHead	-0.26	-6.4e-4	3.2e-4	-2	0.048
Start-Age x ΔBody	-0.22	-6.3e-4	3.7e-4	-1.7	0.096
Start-Age x ΔTail	-0.037	-2.6e-4	1.0e-3	-0.25	0.8
ΔAge x ΔHead	0.072	1.1e-4	2.2e-4	0.5	0.62
ΔAge x ΔBody	0.14	2.0e-4	1.9e-4	1.1	0.29
ΔAge x ΔTail	0.11	4.0e-4	5.0e-4	0.8	0.42
Start-Age x ΔAge x ΔHead	0.33	4.1e-4	1.9e-4	2.2	0.027
Start-Age x ΔAge x ΔBody	0.29	4.2e-4	1.9e-4	2.2	0.032
Start-Age x ΔAge x ΔTail	0.12	4.2e-4	5.5e-4	0.77	0.44

Note: Female is reference sex. For unstandardized betas, volume is in cubic millim eters and age is in years.

were older at T1 (e.g., 11 years, as depicted in Figure 4A), volumetric increases in head and body volume predicted better item-time memory (Body: β=.47, b=.001, *SE* = 4.9e-4, *t*=2.59, *p*=.01; Head: β=.35, *b*=.001, *SE* = 5.1e-4, *t*=1.87, *p*=.06), but was not significant for children who were younger at T1 (e.g., 8 years, as depicted in Figure 4A), despite the appearance of a negative relation (*p*s ≥.17). Change in the tail was not associated with item-time performance (*p*s ≥ .18). Thus, although the normative pattern of volumetric change in this sample was a linear decrease in the head, and a curvilinear in the body volume over time, protracted increases in head and body volume in older children predicted better item-time memory. Parameter estimates for models separating left and right hippocampal structures are also included in Table S4.

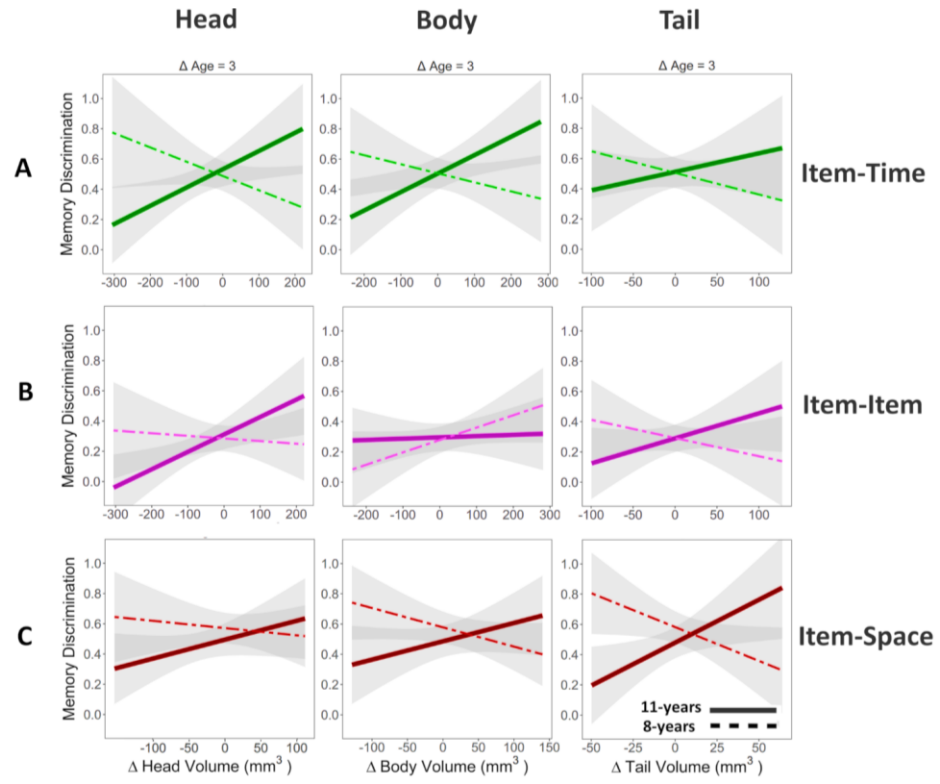

Figure 4. Depicting interaction between change in ICV-corrected volume and cross-sectional differences in the starting age at Time 1 at 8- and 11-years of age evaluated at change in age since Time 1 equaling three years (ΔAge = 3). See Supplemental Figure 1 for depiction of interaction after one year since Time 1; relations between volume changes and memory were stronger at longer delays. Error bands represent 95% confidence intervals**. A.** Item-Time. **B.** Item-Item. **C.** Item-Space.

Item-Item. Consistent with our prediction, changes in hippocampal structure predicted item-item memory. Specifically, we found a significant interaction between volumetric changes in head, body, and tail (as a block) and age at T1 ($\chi2 = 8.82$, $df = 3$, $p = .03$), but this interaction was not significantly moderated by changes in age ($\chi2 = 3.2$, $df = 3$, $p = .37$) (See Table 5). Examining the volumetric change and age at T1 interaction, we found that among children who were young at T1 (i.e., 8 years), increases in body volume predicted greater item-item memory (β=.27, *b*=.0007, *SE* = 2.5e-4, *t*=2.93, *p*=.004). In contrast, among children who were older at T1 (i.e., 11 years), increases in head volume predicted better behavioral performance (β=.24, *b*=.0006, *SE* = 2.3e-4, *t*=2.38, *p*=.02) (See Figure 4B and Figure S1B). Parameter estimates for models separating left and right hippocampal structures are also included in Table S5.

Table 5. Hippocampal Volume Predicting the Development of Item-Item Memory.

	Left and Right Hippocampal Sum				
Effect	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	-	1.2e-1	2.2e-2	5.4	<.0001
Item-Recognition	0.16	1.5e-1	6.2e-2	2.5	0.013
Sex [Male]	-0.0048	-2.1e-3	2.7e-2	-0.077	0.94
Start-Volume Head	-0.013	-1.0e-5	4.7e-5	-0.21	0.83
Start-Volume Body	0.025	2.3e-5	5.6e-5	0.41	0.69
Start-Volume Tail	0.018	2.4e-5	8.2e-5	0.29	0.78
Start-Age	0.2	3.9e-2	1.5e-2	2.6	0.012
ΔAge	0.27	5.5e-2	1.1e-2	5	<.0001
ΔHead	-0.048	-1.2e-4	3.5e-4	-0.35	0.73
ΔBody	-0.00071	-1.7e-6	3.4e-4	-0.005	>0.99
ΔTail	-0.15	-8.7e-4	8.5e-4	-1	0.31
Start-Age x ΔAge	-0.081	-1.1e-2	1.0e-2	-1.1	0.29
Start-Age x ΔHead	0.12	2.5e-4	1.2e-4	2.1	0.039
Start-Age x ΔBody	-0.13	-3.0e-4	1.4e-4	-2.2	0.028
Start-Age x ΔTail	0.015	8.5e-5	3.3e-4	0.26	0.8
ΔAge x ΔHead	0.16	2.1e-4	1.8e-4	1.1	0.26
ΔAge x ΔBody	0.1	1.2e-4	1.6e-4	0.76	0.45
ΔAge x ΔTail	0.13	3.8e-4	4.3e-4	0.88	0.38

Note: Female is reference sex. For unstandardized betas, volume is in cubic millim eters and age is in years.

Overall, volumetric changes in hippocampal body appeared to differentially predict item-time and item-item memory. Consistent with this, we found that the age at T1 by change in body volume interaction was significantly different for item-time and item-item memory ($\chi2 = 8.92$, $df = 1$, $p = .003$). In younger children, the association between change in body and memory was more positive for item-item than item-time (β=.32, *b*=001, *SE* = 5.2e-4, *t*=2.50, *p*=.014), but in older children, there was a trend for a more negative relation for item-item than item-time memory (β=-.28, *b*=-.001, *SE* = 5.8e-4, *t*=-1.93, *p*=.055). Overall results are consistent with the protracted behavioral trajectory of item-item memory and suggest a transition from body to head in supporting developmental improvements in item-item memory.

Item-Space. No significant relations between changes in hippocampal structure and item-space memory were found when we used volume changes summed across hemispheres ($\chi2s \leq 4.04$, $dfs = 3$, $ps \geq .26$) (See Table S6), nor did using overall hippocampal volume perform better than using subregions ($\chi2 = 3.84$, $df = 8$, $p = .87$).

Given the suggestion from the literature that associations between change in head, body, and tail volumes and spatial memory could be right-lateralized, we also tested our model in the right hippocampus. This analysis revealed a significant three-way interaction between changes in right hippocampus, changes in age, and starting age at T1 ($\chi2 = 10.6$, df = 3, $p = .01$) (See Table 6). Volumetric changes significantly more positively predicted memory performance with longer delay (e.g. 3 years; Figure 4C), but not significantly with shorter delays (e.g., 1 year; $ps > .098$; Figure S1C). In other words, in younger children at T1, there was a trend for reduction of tail volume over time predicting better item-space memory (β=-.32, b= -.004, *SE* = .002, *t*=-1.86, *p*=.07), but in older children at T1, volumetric increases in the tail predicted better item-space memory (β=.528, b=.006, *SE* = .003, *t*=2.16, *p*=.03). However, neither the body ($ps \geq .11$) nor

the head ($ps \geq .21$) were significantly associated to item-space memory at those starting ages. Thus, although the hippocampal tail did not seem to show an average pattern of volumetric change based on previous analyses, the present results suggest that individual differences in tail development predict item-space memory performance.

Table 6. Hippocampal Volume Predicting the Development of Item-Space Memory.

	Right Hippocampus				
Effect	**Beta**	***b***	***SE***	***t***	***p***
(Intercept)	-	4.6e-1	0.025	18	<.0001
Item-Recognition	0.31	3.5e-1	7.2e-2	4.8	<.0001
Sex [Male]	-0.083	-4.2e-2	3.2e-2	-1.3	0.19
Start-Volume Head	-0.027	-4.6e-5	1.0e-4	-0.45	0.66
Start-Volume Body	-0.042	-7.6e-5	1.1e-4	-0.68	0.5
Start-Volume Tail	0.039	1.1e-4	1.8e-4	0.61	0.54
Start-Age	0.28	6.3e-2	1.7e-2	3.8	0.0003
ΔAge	0.12	2.9e-2	1.3e-2	2.2	0.028
ΔHead	-0.086	-4.2e-4	6.5e-4	-0.65	0.52
ΔBody	-0.018	-8.3e-5	6.3e-4	-0.13	0.9
ΔTail	-0.14	-1.7e-3	1.7e-3	-0.99	0.32
Start-Age x ΔAge	-0.21	-3.4e-2	1.2e-2	-2.7	0.0077
Start-Age x ΔHead	-0.055	-2.3e-4	5.5e-4	-0.42	0.68
Start-Age x ΔBody	-0.11	-4.7e-4	5.8e-4	-0.81	0.42
Start-Age x ΔTail	-0.33	-4.0e-3	1.8e-3	-2.3	0.025
ΔAge x ΔHead	0.13	3.2e-4	3.6e-4	0.88	0.38
ΔAge x ΔBody	0.025	5.5e-5	3.2e-4	0.17	0.86
ΔAge x ΔTail	0.16	9.6e-4	9.2e-4	1	0.3
Start-Age x ΔAge x ΔHead	0.12	2.4e-4	3.1e-4	0.78	0.44
Start-Age x ΔAge x ΔBody	0.2	4.4e-4	3.2e-4	1.4	0.18
Start-Age x ΔAge x ΔTail	0.41	2.4e-3	9.6e-4	2.5	0.012

Note: Female is reference sex. For unstandardized betas, volume is in cubic millim eters and age is in years.

Discussion

The ability to remember associations between events and their spatio-temporal context depends on hippocampal mechanisms, which bind contextual features into integrated event representations [1]. Here, we asked whether volumetric changes in hippocampal volume predict longitudinal improvements in relational memory, and whether those developmental associations differed depending on hippocampal subregion or type of memory relation.

This is the first report showing that longitudinal improvements in relational memory differed as a function of the type of memory relation, such that item-space memory developed more rapidly than item-time and item-item memory. In the largest longitudinal study of hippocampal subregions to date, this research showed that hippocampal head, body, and tail follow different developmental trajectories from childhood into adolescence. Linking structural and behavioral changes, we report for the first time that volumetric changes in hippocampal head, body, and tail differentially predicted longitudinal improvement in item-space, item-time, and item-item.

Developmental Change in Relational Memory Depends on the Nature of the Relation

In our initial cross-sectional analysis [22], item-space memory reached adults' levels of performance before item-time memory, which in turn preceded item-item memory. In the present research, we examined within-person change while accounting for cross-sectional differences and showed that item-space memory improves until around 10½, whereas item-time and item-item memory followed prolonged trajectories with improvements about 12 and 12½ years of age respectively. This finding is additionally consistent with prior cross-sectional evidence that spatial memory develops earlier than temporal memory [20–22]. Although we cannot rule out the possibility that aspects of our tasks might differ across conditions for reasons other than the type

of relation manipulated, we argue that the use of novel stimuli and arbitrary associations is an effective way to assess relational memory. The more rapid development of item-space memory compared to the other relations suggests that relational memory processes are not fully unitary.

Although item-time memory was generally better than item-item, their developmental trajectories were similar. This may have been due to the dependence of these tasks on shared hippocampal operations. For example, performance on both item-time and item-item memory may have benefitted from some form of temporal processing—the former from processing the precise temporal order of the images and the latter from processing which groups of items were presented together in the same temporal context [7]. On the other hand, there may also be differences in how the hippocampus supports item-time and item-item memory despite the apparent similarity in behavioral trajectory, which may help to explain why item-item is a more challenging task [26,27]. Disentangling these two possibilities was made possible by the longitudinal design combining assessments of both brain and behavior and was addressed in the brain–behavior analyses. Overall, these behavioral findings provide the first longitudinal evidence of protracted and distinct developmental trajectories of different aspects of relational memory. The examination of these relations within participants and within the same task form, which constrain response demands, offers strong support for a functional distinction in relational memory.

Developmental Change in Hippocampal Volumes Varies Along the Anterior-Posterior Axis

We provided new longitudinal evidence indicating that hippocampal head, body, and tail develop differentially from middle childhood into adolescence. Consistent with the findings of the seminal longitudinal study of 31 individuals that first examined morphometric development along the anterior–posterior axis [28], hippocampal head declined in volume from middle

childhood to adolescence, while hippocampal body increased in volume until about 10 years of age and declined thereafter. Hippocampal tail volume was stable throughout middle childhood and adolescence, suggesting that its development occurred earliest, consistent with previous reports [14,16,28].

Curvilinear trajectories in hippocampal development are frequently observed [15,18]. Although not yet definitively linked, volumetric increases may reflect ongoing synaptogenesis and dendritic elaboration, while volumetric declines may reflect synaptic pruning [29]. It is not known why the body, unlike the head and the tail, continues to increase in volume into late childhood (i.e. 9 to 10 years of age). However, the body has been postulated to act as a bridge or integrator of anterior and posterior mechanisms [30]. We can speculate that continued dendritic elaboration in the body, compared to head and tail, may be important for the body to complete the required connections with head and tail. Whatever the reason, the diverging developmental trajectories of head, body, and tail reported here provide a demonstration that the hippocampus is not a uniform structure and joins the growing body of evidence suggesting functional differences along the anterior–posterior hippocampal axis [10].

Changes in Hippocampal Volume Predict Developmental Improvements in Relational Memory

We found evidence that increases in hippocampal volumes over time predicted longitudinal improvements in relational memory. We note that these positive relations with behavior are observed even in the context of normative volumetric decreases (e.g., hippocampal head). Previous cross-sectional studies have reported negative associations between hippocampal head volume and behavior [14,17], suggesting the hypothesis that decreases of hippocampal head over time may promote behavioral improvements. Instead, even though we confirmed normative

354 volumetric declines in this region during development, greater memory performance was
355 observed among those with a relative *increase* in volume. These findings may shed light on
356 underlying mechanisms. One possibility is that these positive associations may depend on
357 ongoing synaptogenesis and dendritic elaboration within hippocampal circuitry [31] and these
358 processes may be particularly important for behavior, even when other mechanisms of structural
359 change, such as pruning, may result in a net loss of volume. Our findings overall support a
360 nascent body of cross-sectional research obtained over the last decade linking the hippocampus
361 to age differences in memory [13,14]. These findings dispel a long-held, but not adequately tested
362 assumption, that the hippocampus and the associative processes it supports, do not contribute to
363 developmental improvements in memory after early childhood [19].

364 We also assessed, for the first time, whether the longitudinal association between
365 hippocampal structure and memory differed as a function of subregion and type of memory
366 relation. These analyses revealed distinct associations, suggesting that processes supporting
367 memory for item-space, item-time, and item-item relations are not uniform across the anterior-
368 posterior axis of the structure. Bilateral increases in the volume of hippocampal head and body
369 predicted larger improvement in item-time memory in older children. In contrast, increases in
370 body volumes predicted item-item memory in younger children and increases in head volume
371 predicted better item-item memory in older children, suggesting a developmental transition from
372 body to head for this type of relation. Finally, the relation between volumetric changes and the
373 development of item-space memory was right lateralized and restricted to the tail, increases in
374 right hippocampal tail over time predicted greater item-space memory, particularly in older
375 children.

Overall, these data suggest that protracted increase in sub-regional volumes are associated with behavioral improvement. It is somewhat surprising that we did not detect reliable relations between hippocampal growth and memory in younger children for item-time and item-space memory. It is possible that memory improvements in younger compared to older children reflect not only change in relational memory, but also increased consistency in children's engagement with the memory task, potentially obscuring relations between memory and volumetric change. However, contrary to this possibility, we found an association between increases in hippocampal body in younger children and item-item memory, the most difficult of the three relational tasks and, potentially, the most likely to produce less consistent data. Nevertheless, we cannot exclude that our *change in age* parameter captured more variance than our *change in volume parameter* because of additional processing demands in young children. Change in age was included to model time and account for any source of development due to extra hippocampal processes, but shared variance with measures of hippocampal development cannot be excluded.

Our results are consistent with prior evidence that the hippocampus supports memory for item-space, item-time, and item-item relations [6,8], but also indicate heterogeneity in how each subregion contributes to these memory relations. Memory for temporal order reliably recruits the hippocampus in functional neuroimaging studies [3]; however, while we only observed relations with item-time memory for the hippocampal head and body, associations with hippocampal tail have also been reported [32], suggesting that temporal memory may not be strongly localized to any anterior-posterior subregion. Memory for associations between items has been preferentially associated with hippocampal head and body [4,11], and our results are consistent with these findings. It is notable that item-time and item-item memory trajectories were similar

399 behaviorally. Yet, their trajectories were support by different hippocampal subregions
400 underscoring the advantage of a longitudinal design. Finally, spatial memory is frequently
401 associated with posterior hippocampus (i.e. tail and body) [12]. We found evidence consistent with
402 this suggestion restricted to the right tail.

403 Many open questions remain about the processes that might underlie these different
404 longitudinal structure-behavior relations. One possibility is that hippocampal head, body, and tail
405 differ in terms of cell types and genetic expression [33], synaptic plasticity [34], and relative
406 cytoarchitectural composition (i.e. dentate gyrus, CA 1,3)[15,16] For example, there is some
407 evidence for a division of time and space in some cytoarchitectural circuits [3]. Another possibility
408 is that each subregion supports the same set of operations via the tri-synaptic circuit, but on
409 different types of information received through differential connections with extrahippocampal
410 brain regions. More anterior subregions exhibit greater functional connectivity with perirhinal
411 cortex, while more middle and posterior regions of the hippocampus exhibit greater functional
412 connectivity with posterior parahippocampal cortex [35]. The perirhinal cortex is widely
413 recognized as a region supporting complex item representations, while posterior
414 parahippocampal cortex may support spatial and non-spatial contextual associations [5]. A third
415 possibility is that the differences we observed reflect more general divisions of labor that
416 transcend the type of relation examined [10,17]. Although we have no reason to suspect that our
417 item-time and item-item tasks required more generalization processes (as suggested by being the
418 only tasks associated with changes in hippocampal head), the current study cannot exclude this
419 possibility directly. Future research is required to disentangle these possibilities.

420 The present research has several limitations. One potential limitation is that we did not
421 differentiate between encoding and retrieval operations, and thus we cannot address hypotheses

that anterior and posterior hippocampus preferentially support encoding and retrieval, respectively [36]. However, it is not clear how differential support for encoding or retrieval operations could explain the structure-behavior relations we observed here, especially given identical encoding procedures, and minimization of retrieval demands using short-term memory delays. Another potential limitation is that we focused exclusively on the development of the hippocampus, while extra-hippocampal changes can additionally account for memory changes. However, the goal of this research was to examine relational memory processes in the hippocampus in a task that manipulated the type of relation. Moreover, our task used materials and procedures designed to ensure that differences in performance across relational conditions depended more strongly on hippocampally mediated associative processes [6,8] than on pre-frontally mediated strategic or controlled processes [37–39]. These procedures included identical encoding procedures across relational conditions, the use of novel objects, which could not easily be labeled, and arbitrary relations among them. As discussed earlier, retrieval demands were reduced by testing memory over short delays. Finally, this research did not address how cytoarchitectural subfields in the hippocampus (i.e. dentate gyrus, CA 1-3) may account for the relations with head, body, and tail development, which should be the subject of future research and analysis.

In conclusion, we present the first evidence to establish distinct links between subregional changes in hippocampal structure to the differential development of relational memory for associations between items and space, time, and other items. These results—beyond their implication to theories of memory development—begin to disentangle the contributions of the hippocampus to three critical dimensions of relational memory.

Materials and Methods

Participants

Our sample included 171 participants at T1 (84 females; 143 behavioral assessments; 155 structural scans; M_{age} = 9.45 years, SD_{age} = 1.09, 7.1 – 12.0 years), 140 participants at T2 (66 females; 136 behavioral assessments, 118 structural scans; M_{age} = 10.86 years, SD_{age} = 1.22, 8.2 – 13.86 years), and 119 participants at T3 (52 females; 114 behavioral assessments, 88 structural scans; M_{age} = 12.12 years, SD_{age} = 1.31, 9.0 – 15.16 years). Item-space, item-time, and item-item memory at T1 did not significantly differ between those who returned at T2 compared to those who did not (χ^2 = 2.61, *df* =3, *p* = .46 uncorrected), or between participants who returned for T3 and those who did not (χ^2 = 1.31, *df* =3, *p* = .73 uncorrected). Head, body, and tail volumes did not differ at T1 in those who returned at T2 than those who did not (χ^2s$\leq$ 1.17, *df*s =2, *p*s $\geq$ .56 uncorrected), or between participants who returned for T3 and those who did not (χ^2s$\leq$ 2.13, *df* s = 2, *p*s $\geq$ .34 uncorrected). Children were ineligible if parents reported a learning disability, neurological or psychological diagnosis requiring medication at the time of enrollment. Children were compensated for their participation. This research was conducted with the approval of the Institutional Review Board at the University of California, Davis.

Materials and Procedures

Behavioral and imaging data were collected over two visits. The Triplet Binding Task (TBT) was administered on the first visit. Magnetic Resonance Imaging (MRI) occurred approximately one week after the behavioral assessment.

Triplet Binding Task. The TBT is a memory task that assesses item-time, item-space, and item-item relational memory and item-recognition memory using [6,22]. To counter fatigue, the

TBT was administered over two separate sessions on the same day. In each session, each memory type was assessed in blocks to minimize increased task-switching costs in younger children. Blocks were counterbalanced across participants. Within each assessment block, 5 encoding-retrieval phases were administered. TBT stimuli included color images of novel and obscure real-world objects unlikely to be familiar to participants; these stimuli limit the utility of semantic-based organizational memory strategies known to underlie some developmental improvements in memory [37].

Encoding Phase. Prior to each testing block, participants were instructed and tested on their understanding of the task, the relation to be encoded, and the triplet trial structure using practice encoding and retrieval phases. The encoding phase format was identical for item-time, item-space, item-item, and item-recognition encoding conditions. Each encoding phase comprised three trials. In each trial, three novel objects (i.e. triplet) were sequentially presented for one second to three locations on a computer screen, one object per location (see Figure 1B Top). A one second inter-trial fixation was then presented before proceeding to the next of the three encoding trials. To aid learning, the encoding phase was repeated a second time.

Retrieval Phase. Retrieval immediately followed each encoding phase. Each retrieval phase, depending on the testing block, assessed memory for item-space, item-time, or item-item relations, or item recognition memory (Figure 1B Bottom). The retrieval phase comprised three target and/or lure probes. Overall, 15 targets and 15 lures were probed in each retrieval condition.

Item-space. In each item-space test probe, three objects from the same encoding trial appeared together on the screen. Participants decided whether all objects appeared at their original positions or not. In target trials all objects maintain their original positions, while in lure

trials the spatial positions of two objects are exchanged.

Item-time. In each item-time retrieval phase, three objects from the same encoding trial were sequentially presented to the center of the screen. No object appeared at their original spatial position. Participants decided whether the sequence of objects in the probe appeared in their original order or not. In target trials all objects maintain their original order, while in lure trials the ordinal position of two objects are switched.

Item-item. In each item-item test probe, three objects appeared on the screen at three horizontal positions. No object appeared at their original spatial position. Participants decided whether all objects had appeared together in the same trial (i.e. triplet) or not. In target trials all objects came from the same encoding trial, while in lure trials one object was exchanged with an object from another trial from the same encoding phase.

***Item recognition*.** In each item-recognition test probe, three objects appeared together on the screen at three horizontal positions. No object appeared at their original spatial position. Participants decided whether all objects had previously been studied. In target trials all objects were studied, while in lure trials two of the three objects were new.

Magnetic Resonant Imaging. Magnetic Resonance Imaging (MRI) was acquired at the University of California, Davis Imaging Research Center in a 3T Siemens Tim Trio scanner with a 32-channel head coil. Two 7½-minute T1-weighted MPRAGE images were acquired (TE: 3.2 ms; TR: 2500 ms; in-plane resolution: 640 × 256 matrix, 0.35 mm x 0.70 mm; slice resolution: 640, 0.35 mm). Each participant's two structural images were co-registered, averaged, and oriented so that the coronal plane was perpendicular to the long axis of the hippocampus. Each image was cropped into left and right hippocampal regions, after which retrospective bias correction was performed.

Hippocampal Segmentation. Hippocampal segmentation was performed using the Automatic Hippocampal Estimator using Atlas-based Delineation (AHEAD) software which implements a state-of-the-art multi-atlas joint label fusion approach to image segmentation [40]. Briefly, manually labeled atlases of left and right hippocampus are non-linearly registered to each participant's structural image using Advanced Normalization Tools. This produces candidate segmentations for each target's hippocampus from which a consensus segmentation is computed using joint label fusion, an advanced weighted voting procedure [40]. The multi-atlas of the hippocampus was produced by expert manual rater (JKL) in 14 children balanced for sex and age using an established protocol [41], a quantity of atlases sufficient to yield high accuracy segmentation [42]. Each segmentation was manually reviewed for accuracy.

Delineation of Hippocampal Sub-Regions. Head, body, and tail subregions were delineated by blinded rater PD and JKL under an established protocol [14]. Each subregion volume was adjusted by estimated intracranial volume (ICV) using the analysis of covariance approach [24]. ICV estimates were obtained using previously described procedures [15].

Analytical Approach

All analyses used mixed random effect models capable of accounting for within-subject dependencies in the data [23]. Since accelerated longitudinal designs enroll participants across a range of starting ages, the effects of age comprise both the within-individual effect of age change and the between-subject effect of cross-sectional differences in age. We therefore followed the approach in which the effects of age at each time point are separated into a within-subject time-varying covariate (i.e. change in age since T1) and a between-subject time-invariant covariate (i.e. starting age at T1) [23,25]. Given that at most only three measurement occasions were available, we did not estimate non-linear within-subject effects. However, we capitalize on the

accelerated longitudinal design to test whether children of different starting ages have different within-subject trajectories. Time invariant covariates (e.g., starting age at T1) were centered at the mean of the measure at the T1. All mixed effect models included a random intercept and random slope for change in age since T1. Estimation of model parameters used restricted maximum likelihood (REML), while model comparisons used maximum likelihood (ML). Data were inspected for univariate and multivariate outliers using distribution-based outlier detection, data and Q-Q plots, Z-scoring, and Cook's distance; outlying volume changes were identified and Winsorized at the 2nd and 98th percentiles. Mixed models were fitted and plotted using the lme4 (ver. 1.1), lmerTest (ver. 2.0) and effects (ver. 3.1) packages in R (ver. 3.3.1). Model comparisons were used to build up each model over baseline models, beginning with first-order effects and systematically testing inclusion of higher order interaction effects.

Behavioral Model. Memory scores were computed at each time point and relation as the difference between hit and false alarm rates. Models include the effects of starting age at T1, change in age, and memory relation, and control for effects of sex and item-recognition at T1. The full behavioral model is described in Table 1.

Hippocampal Model. We tested for main and interactive effects of starting age at T1, change in age, and hippocampal subregion, and control for effects of sex and hemisphere. The hippocampal model is described in Table 1. We also computed partial derivatives to derive the starting age at T1 in which the slope of change in age would be predicted to equal zero (i.e., the apex/base of the trajectories).

Brain-Behavior Model. Brain-behavior analyses examined item-time, item-space, and item-item memory separately. Each model simultaneously tested the effects of changes in hippocampal head, body, and tail on memory performance, while accounting for their volumes at

T1. The brain-behavior model is described in Table 1. Model comparisons tested the effect of head, body, and tail changes together as a block, building up the model. We began by testing the change in model fit by simultaneously adding the three volume changes (as a block) over a baseline model, which included age at T1, change in age, item-recognition at T1. We then proceeded by testing the change in fit by adding the two-way interactions between changes head, body, and tail volume and change in age since T1, as a block. Likewise, the two-way interactions changes in head, body, and tail volumes with the age at T1. Lastly, we tested the change in model fit by adding the three-way interactions between changes in head, body, and tail volumes with change in age and age at T1. Finally, primary analyses summed volumes across hemispheres. Additional analyses considering left and right hippocampal structures separately were also conducted.

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Declarations

The authors have no financial or non-financial competing interests to declare.

References

1. Eichenbaum, H. & Cohen, N. J. *From conditioning to conscious recollection memory systems of the brain*. (Oxford University Press, 2001).
2. Ekstrom, A. D., Copara, M. S., Isham, E. A., Wang, W. & Yonelinas, A. P. Dissociable networks involved in spatial and temporal order source retrieval. *NeuroImage* **56**, 1803–1813 (2011).

583 3. Eichenbaum, H. Memory on time. *Trends Cogn. Sci. (Regul. Ed.)* **17**, 81–88 (2013).
584 4. Giovanello, K. S., Schnyer, D. M. & Verfaellie, M. A critical role for the anterior
585 hippocampus in relational memory: evidence from an fMRI study comparing associative and
586 item recognition. *Hippocampus* **14**, 5–8 (2004).
587 5. Ranganath, C. Binding Items and Contexts: The Cognitive Neuroscience of Episodic
588 Memory. *Curr Dir Psychol Sci* **19**, 131–137 (2010).
589 6. Konkel, A., Warren, D. E., Duff, M. C., Tranel, D. N. & Cohen, N. J. Hippocampal amnesia
590 impairs all manner of relational memory. *Front Hum Neurosci* **2**, 15 (2008).
591 7. Davachi, L. & DuBrow, S. How the hippocampus preserves order: the role of prediction and
592 context. *Trends Cogn. Sci. (Regul. Ed.)* **19**, 92–99 (2015).
593 8. Konkel, A. & Cohen, N. J. Relational Memory and the Hippocampus: Representations and
594 Methods. *Front Neurosci* **3**, 166–174 (2009).
595 9. Moser, E., Moser, M. B. & Andersen, P. Spatial learning impairment parallels the magnitude
596 of dorsal hippocampal lesions, but is hardly present following ventral lesions. *J. Neurosci.*
597 **13**, 3916–3925 (1993).
598 10. Poppenk, J. & Moscovitch, M. A hippocampal marker of recollection memory ability among
599 healthy young adults: contributions of posterior and anterior segments. *Neuron* **72**, 931–937
600 (2011).
601 11. Giovanello, K. S., Schnyer, D. & Verfaellie, M. Distinct hippocampal regions make unique
602 contributions to relational memory. *Hippocampus* **19**, 111–117 (2009).
603 12. Persson, J., Stening, E., Nordin, K. & Söderlund, H. Predicting episodic and spatial memory
604 performance from hippocampal resting-state functional connectivity: Evidence for an
605 anterior-posterior division of function. *Hippocampus* **28**, 53–66 (2018).

606 13. Daugherty, A. M., Bender, A. R., Raz, N. & Ofen, N. Age differences in hippocampal
607 subfield volumes from childhood to late adulthood. *Hippocampus* **26**, 220–228 (2016).
608 14. DeMaster, D., Pathman, T., Lee, J. K. & Ghetti, S. Structural development of the
609 hippocampus and episodic memory: developmental differences along the anterior/posterior
610 axis. *Cereb. Cortex* **24**, 3036–3045 (2014).
611 15. Lee, J. K., Ekstrom, A. D. & Ghetti, S. Volume of hippocampal subfields and episodic
612 memory in childhood and adolescence. *Neuroimage* **94**, 162–171 (2014).
613 16. Riggins, T. *et al.* Protracted hippocampal development is associated with age-related
614 improvements in memory during early childhood. *Neuroimage* **174**, 127–137 (2018).
615 17. Schlichting, M. L., Guarino, K. F., Schapiro, A. C., Turk-Browne, N. B. & Preston, A. R.
616 Hippocampal Structure Predicts Statistical Learning and Associative Inference Abilities
617 during Development. *J Cogn Neurosci* **29**, 37–51 (2017).
618 18. Lee, J. K., Johnson, E. G. & Ghetti, S. Hippocampal development: Structure, function and
619 implications. in *The hippocampus from cells to systems: Structure, connectivity, and*
620 *functional contributions to memory and flexible cognition* 141–166 (Springer International
621 Publishing, 2017). doi:10.1007/978-3-319-50406-3_6
622 19. Ghetti, S. & Lee, J. Children's episodic memory. *Wiley Interdisciplinary Reviews: Cognitive*
623 *Science* **2**, 365–373 (2011).
624 20. Guillery-Girard, B. *et al.* Developmental trajectories of associative memory from childhood
625 to adulthood: a behavioral and neuroimaging study. *Front Behav Neurosci* **7**, 126 (2013).
626 21. Picard, L., Cousin, S., Guillery-Girard, B., Eustache, F. & Piolino, P. How do the different
627 components of episodic memory develop? Role of executive functions and short-term
628 feature-binding abilities. *Child Dev* **83**, 1037–1050 (2012).

629 22. Lee, J. K., Wendelken, C., Bunge, S. A. & Ghetti, S. A Time and Place for Everything:
630 Developmental Differences in the Building Blocks of Episodic Memory. *Child Dev* **87**, 194–
631 210 (2016).
632 23. Hoffman, L. *Longitudinal Analysis : Modeling Within-Person Fluctuation and Change*.
633 (Routledge, 2015). doi:10.4324/9781315744094
634 24. Raz, N. *et al.* Regional brain changes in aging healthy adults: general trends, individual
635 differences and modifiers. *Cereb. Cortex* **15**, 1676–1689 (2005).
636 25. Sliwinski, M., Hoffman, L. & Hofer, S. M. Evaluating Convergence of Within-Person
637 Change and Between-Person Age Differences in Age-Heterogeneous Longitudinal Studies.
638 *Res Hum Dev* **7**, 45–60 (2010).
639 26. Pathman, T. & Ghetti, S. The eyes know time: a novel paradigm to reveal the development
640 of temporal memory. *Child Dev* **85**, 792–807 (2014).
641 27. Pathman, T. & Ghetti, S. Eye Movements Provide an Index of Veridical Memory for
642 Temporal Order. *PLoS One* **10**, (2015).
643 28. Gogtay, N. *et al.* Dynamic mapping of normal human hippocampal development.
644 *Hippocampus* **16**, 664–672 (2006).
645 29. Stiles, J. & Jernigan, T. L. The basics of brain development. *Neuropsychol Rev* **20**, 327–348
646 (2010).
647 30. Bast, T., Wilson, I. A., Witter, M. P. & Morris, R. G. M. From rapid place learning to
648 behavioral performance: a key role for the intermediate hippocampus. *PLoS Biol.* **7**,
649 e1000089 (2009).
650 31. Huttenlocher, P. R. & Dabholkar, A. S. Regional differences in synaptogenesis in human
651 cerebral cortex. *J. Comp. Neurol.* **387**, 167–178 (1997).

652 32. Roberts, B. M., Libby, L. A., Inhoff, M. C. & Ranganath, C. Brain activity related to
653 working memory for temporal order and object information. *Behav. Brain Res.* **354**, 55–63
654 (2018).
655 33. Cembrowski, M. S. *et al.* Spatial Gene-Expression Gradients Underlie Prominent
656 Heterogeneity of CA1 Pyramidal Neurons. *Neuron* **89**, 351–368 (2016).
657 34. Babiec, W. E., Jami, S. A., Guglietta, R., Chen, P. B. & O'Dell, T. J. Differential Regulation
658 of NMDA Receptor-Mediated Transmission by SK Channels Underlies Dorsal-Ventral
659 Differences in Dynamics of Schaffer Collateral Synaptic Function. *J. Neurosci.* **37**, 1950–
660 1964 (2017).
661 35. Preston, A. R. & Eichenbaum, H. Interplay of hippocampus and prefrontal cortex in
662 memory. *Curr. Biol.* **23**, R764-773 (2013).
663 36. Kim, H. Encoding and retrieval along the long axis of the hippocampus and their
664 relationships with dorsal attention and default mode networks: The HERNET model.
665 *Hippocampus* **25**, 500–510 (2015).
666 37. Bjorklund, D. F., Dukes, C. & Brown, R. D. The development of memory strategies. in *The*
667 *development of memory in infancy and childhood, 2nd ed* 145–175 (Psychology Press,
668 2009).
669 38. Ghetti, S. & Angelini, L. The development of recollection and familiarity in childhood and
670 adolescence: evidence from the dual-process signal detection model. *Child Dev* **79**, 339–358
671 (2008).
672 39. Shing, Y. L. *et al.* Episodic memory across the lifespan: The contributions of associative and
673 strategic components. *Neuroscience & Biobehavioral Reviews* **34**, 1080–1091 (2010).

40. Wang, H. & Yushkevich, P. A. Multi-atlas segmentation with joint label fusion and corrective learning—an open source implementation. *Front Neuroinform* **7**, (2013).

41. Lee, J. K. *et al.* Assessing hippocampal development and language in early childhood: Evidence from a new application of the Automatic Segmentation Adapter Tool. *Hum Brain Mapp* **36**, 4483–4496 (2015).

42. Asman, A. J. & Landman, B. A. Non-local statistical label fusion for multi-atlas segmentation. *Med Image Anal* **17**, 194–208 (2013).

Supplementary Information

Figure S1 Related to Figure 4. Depicting interaction between change in ICV-corrected volume and cross-sectional differences in the starting age at Time 1 at 8- and 11-years of age evaluated at a change in age since Time 1 equaling one year (ΔAge = 1). See Figure 4 for depiction of interaction after three years since Time 1; smaller changes in age corresponded to smaller differences in memory with increased sub-region ICV-corrected volume. **A.** Item-Time. **B.** Item-Item. **C.** Item-Space.

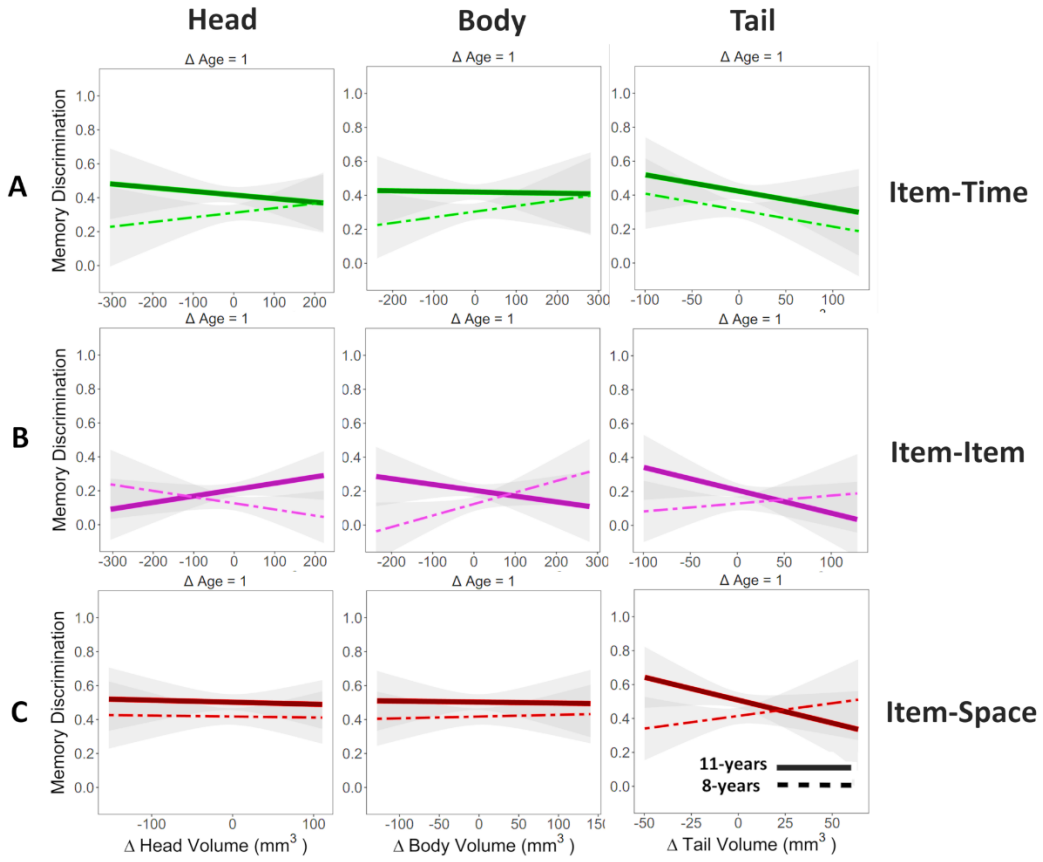

Table S1 Related to Table 2 and Figure 2. Relational Memory Development

Effect	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	–	.453	.020	22.9	<.0001
Item-Recognition (Mean-Centered)	.244	.294	.048	5.98	<.0001
Male	-.049	-.026	.021	-1.24	.223
Start-Age (Mean-Centered)	.183	.039	.013	3.07	.002
ΔAge	.091	.023	.011	2.14	.033
Item-Time	-.218	-.124	.019	-6.62	<.0001
Item-Item	-.548	-.311	.019	-16.7	<.0001
Start-Age x ΔAge	-.124	-.019	.009	-2.20	.029
Start-Age x Item-Time	.021	.008	.014	.540	.590
Start-Age x Item-Item	.027	-.010	.014	-.705	.482
ΔAge x Item-Time	.079	.028	.013	2.19	.029
ΔAge x Item-Item	.081	.027	.013	2.12	.034
Start-Age x ΔAge x Item-Time	.003	.0007	.011	.066	.950
Start-Age x ΔAge x Item-Item	.002	.0006	.011	.061	.951

Model Fit of Fixed Effects: $\chi 2$=464.3, *df*=13, $p < 2.2e\text{-}16$; Interactions with sex were not significant, $\chi 2s \leq 4.66$, *df*s=3, *p*s≥.20. Item-Space and female are referen ce categories. Thus, ΔAge and Start-Age x ΔAge represents development of Item -Space.

Table S2 Related to Table 3. Subregional Differences in Hippocampal Development

Effect	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	–	1270	10.0	127	<.0001
Male	.0008	-2.08	11.7	-.178	.862
Right Hemisphere	-.031	24.8	4.62	5.38	<.0001
Start-Age (Mean-Centered)	.013	1.41	6.85	.206	.842
ΔAge	.006	3.20	3.86	.830	.411
Hippocampal Head	-.151	-91.3	7.97	-11.5	<.0001
Hippocampal Tail	-1.02	-1069	7.89	-136	<.0001
Start-Age x ΔAge	-.031	-9.19	3.64	-2.53	.012
Start-Age x Head	-.005	2.66	7.13	.373	.711
Start-Age x Tail	-.014	-7.04	7.06	-.997	.322
ΔAge x Head	-.022	-12.6	5.27	-2.39	.017
ΔAge x Tail	.002	.256	5.23	.049	.960
Start-Age x ΔAge x Head	.012	5.01	4.97	1.01	.312
Start-Age x ΔAge x Tail	.024	12.8	4.94	2.59	.010

Model Fit of Fixed Effects: $\chi 2$=6,304, *df*=13, $p < 2.2e\text{-}16$; Interactions with hemisphere not significant: $\chi 2$=4.97, *df*=9, *p*=.84. Note: Female and hippocampal body are reference categories. Thus, ΔAge and Start-Age x ΔAge represents development of the body.

Table S3 Related to Table 3. Development of Total Hippocampal Volume

Effect	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	–	2651	25.5	104	<.001
Male	.013	5.95	34.9	.170	0.86
Right Hemisphere	.167	78.0	6.82	11.4	<.001
Start-Age (Mean-Centered)	.007	1.31	15.8	.083	.932
ΔAge	-.023	-5.50	3.94	-1.40	.174
Start-Age x ΔAge	-.053	-7.69	3.73	-2.06	.042

Model Fit of Fixed Effects: $\chi 2$=119.7, *df*=5, *p*<2.2e-16. Note: Interactions with hemisphere not significant: $\chi 2$=6.95, *df*=5, *p* =.22; Female and left hemisphere are reference categories.

Table S4 Related to Figure 4. Hippocampal Volume Predicting the Development of Item-Time Memory.

	Left Hippocampus					Right Hippocampus					· Left and Right Hippocampal Sum				
Effect	**Beta**	**b**	***SE***	***t***	***p***	**Beta**	***b***	***SE***	***t***	***p***	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	-	3.1e-1	2.6e-2	12	<.0001	-	3.2e-1	2.6e-2	12	<.0001	-	3.2e-1	2.5e-2	13	<.0001
Item-Recognition	0.29	3.3e-1	7.3e-2	4.5	<.0001	0.27	3.1e-1	7.4e-2	4.3	<.0001	0.28	3.2e-1	7.4e-2	4.4	<.0001
Sex [Male]	-0.041	-2.1e-2	3.3e-2	-0.65	0.52	-0.061	-3.2e-2	3.2e-2	-0.99	0.33	-0.053	-2.8e-2	3.2e-2	-0.86	0.39
Start-Volume Head	-0.093	-1.5e-4	1.0e-4	-1.5	0.14	-0.018	-3.1e-5	1.1e-4	-0.29	0.77	-0.049	-4.5e-5	5.6e-5	-0.79	0.43
Start-Volume Body	-0.028	-5.6e-5	1.2e-4	-0.45	0.65	-0.097	-1.8e-4	1.1e-4	-1.6	0.12	-0.065	-7.0e-5	6.6e-5	-1.1	0.29
Start-Volume Tail	0.074	2.2e-4	1.8e-4	1.2	0.24	0.044	1.3e-4	1.9e-4	0.69	0.49	0.062	9.8e-5	9.9e-5	0.99	0.32
Start-Age	0.24	5.6e-2	1.7e-2	3.3	0.0014	0.25	6.0e-2	1.7e-2	3.4	0.00076	0.25	5.8e-2	1.7e-2	3.4	0.001
ΔAge	0.25	6.0e-2	1.3e-2	4.7	<.0001	0.27	6.5e-2	1.3e-2	5.2	<.0001	0.26	6.2e-2	1.3e-2	4.7	<.0001
ΔHead	-0.11	-4.9e-4	6.1e-4	-0.81	0.42	-0.12	-6.0e-4	6.5e-4	-0.92	0.36	-0.063	-1.9e-4	4.1e-4	-0.47	0.64
ΔBody	-0.2	-9.6e-4	6.5e-4	-1.5	0.14	0.02	9.5e-5	6.3e-4	0.15	0.88	-0.056	-1.6e-4	3.8e-4	-0.43	0.67
ΔTail	-0.25	-2.9e-3	1.5e-3	-2	0.05	-0.13	-1.6e-3	1.7e-3	-0.95	0.34	-0.2	-1.4e-3	9.5e-4	-1.5	0.14
Start-Age x ΔAge	-0.092	-1.5e-2	1.2e-2	-1.3	0.21	-0.15	-2.4e-2	1.2e-2	-2	0.044	-0.13	-2.1e-2	1.2e-2	-1.7	0.095
Start-Age x ΔHead	-0.34	-1.4e-3	5.5e-4	-2.5	0.014	-0.22	-9.5e-4	5.5e-4	-1.7	0.084	-0.26	-6.4e-4	3.2e-4	-2	0.048
Start-Age x ΔBody	-0.3	-1.4e-3	6.6e-4	-2.1	0.035	-0.22	-9.4e-4	5.8e-4	-1.6	0.11	-0.22	-6.3e-4	3.7e-4	-1.7	0.096
Start-Age x ΔTail	-0.001	-1.1e-5	1.4e-3	-0.008	0.99	-0.078	-9.5e-4	1.8e-3	-0.54	0.59	-0.037	-2.6e-4	1.0e-3	-0.25	0.8
ΔAge x ΔHead	0.12	2.8e-4	3.1e-4	0.89	0.37	0.18	4.6e-4	3.6e-4	1.3	0.2	0.072	1.1e-4	2.2e-4	0.5	0.62
ΔAge x ΔBody	0.31	7.0e-4	3.3e-4	2.1	0.035	0.004	9.1e-6	3.1e-4	0.029	0.98	0.14	2.0e-4	1.9e-4	1.1	0.29
ΔAge x ΔTail	0.15	8.7e-4	7.9e-4	1.1	0.27	0.11	6.4e-4	9.0e-4	0.71	0.48	0.11	4.0e-4	5.0e-4	0.8	0.42
Start-Age x ΔAge x ΔHead	0.4	8.4e-4	2.9e-4	2.9	0.0042	0.29	6.4e-4	3.1e-4	2.1	0.038	0.33	4.1e-4	1.9e-4	2.2	0.027
Start-Age x ΔAge x ΔBody	0.35	8.4e-4	3.5e-4	2.4	0.018	0.31	7.0e-4	3.2e-4	2.2	0.028	0.29	4.2e-4	1.9e-4	2.2	0.032
Start-Age x ΔAge x ΔTail	0.032	1.8e-4	7.3e-4	0.25	0.81	0.22	1.4e-3	9.4e-4	1.5	0.15	0.12	4.2e-4	5.5e-4	0.77	0.44

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

Table S5 Related to Figure 4. Hippocampal Volume Predicting the Development of Item-Item Memory.

	Left Hippocampus					Right Hippocampus					· Left and Right Hippocampal Sum				
Effect	**Beta**	**b**	***SE***	***t***	***p***	**Beta**	***b***	***SE***	***t***	***p***	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	-	1.2e-1	2.3e-2	5.3	<.0001	-	1.2e-1	2.3e-2	5.2	<.0001	-	1.2e-1	2.2e-2	5.4	<.0001
Item-Recognition	0.15	1.4e-1	6.1e-2	2.4	0.019	0.15	1.4e-1	6.2e-2	2.3	0.024	0.16	1.5e-1	6.2e-2	2.5	0.013
Sex [Male]	-0.015	-6.6e-3	2.7e-2	-0.24	0.81	-8.2e-05	-3.6e-5	2.7e-2	-0.001	0.99	-0.0048	-2.1e-3	2.7e-2	-0.077	0.94
Start-Volume Head	-0.018	-2.5e-5	8.6e-5	-0.29	0.77	-0.011	-1.6e-5	8.9e-5	-0.18	0.85	-0.013	-1.0e-5	4.7e-5	-0.21	0.83
Start-Volume Body	-0.012	-2.1e-5	1.0e-4	-0.2	0.84	0.025	3.9e-5	9.7e-5	0.4	0.69	0.025	2.3e-5	5.6e-5	0.41	0.69
Start-Volume Tail	0.034	8.3e-5	1.5e-4	0.55	0.59	0.0012	2.9e-6	1.6e-4	0.019	0.99	0.018	2.4e-5	8.2e-5	0.29	0.78
Start-Age	0.21	4.2e-2	1.5e-2	2.7	0.0068	0.2	3.8e-2	1.5e-2	2.5	0.014	0.2	3.9e-2	1.5e-2	2.6	0.012
ΔAge	0.25	5.1e-2	1.1e-2	4.7	<.0001	0.27	5.5e-2	1.1e-2	5.2	<.0001	0.27	5.5e-2	1.1e-2	5	<.0001
ΔHead	0.026	1.0e-4	5.4e-4	0.19	0.85	-0.13	-5.5e-4	5.8e-4	-0.94	0.35	-0.048	-1.2e-4	3.5e-4	-0.35	0.73
ΔBody	-0.19	-7.4e-4	5.8e-4	-1.3	0.2	0.1	4.1e-4	5.5e-4	0.74	0.46	-0.00071	-1.7e-6	3.4e-4	-0.005	1
ΔTail	-0.068	-6.6e-4	1.3e-3	-0.5	0.62	-0.14	-1.4e-3	1.5e-3	-0.95	0.34	-0.15	-8.7e-4	8.5e-4	-1	0.31
Start-Age x ΔAge	-0.11	-1.5e-2	1.0e-2	-1.5	0.15	-0.11	-1.5e-2	1.0e-2	-1.4	0.16	-0.081	-1.1e-2	1.0e-2	-1.1	0.29
Start-Age x ΔHead	0.075	2.5e-4	2.0e-4	1.3	0.2	0.062	2.2e-4	2.0e-4	1.1	0.28	0.12	2.5e-4	1.2e-4	2.1	0.039
Start-Age x ΔBody	-0.12	-4.9e-4	2.2e-4	-2.2	0.029	-0.06	-2.2e-4	2.2e-4	-1	0.32	-0.13	-3.0e-4	1.4e-4	-2.2	0.028
Start-Age x ΔTail	0.01	9.0e-5	5.0e-4	0.18	0.86	0.034	3.5e-4	5.8e-4	0.6	0.55	0.015	8.5e-5	3.3e-4	0.26	0.8
ΔAge x ΔHead	0.1	1.9e-4	2.7e-4	0.71	0.48	0.25	5.2e-4	3.0e-4	1.7	0.087	0.17	2.1e-4	1.8e-4	1.1	0.26
ΔAge x ΔBody	0.34	6.5e-4	2.8e-4	2.3	0.022	-0.027	-5.1e-5	2.6e-4	-0.2	0.85	0.1	1.2e-4	1.6e-4	0.76	0.45
ΔAge x ΔTail	0.068	3.4e-4	6.7e-4	0.51	0.61	0.11	5.4e-4	7.6e-4	0.72	0.48	0.13	3.8e-4	4.3e-4	0.88	0.38

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

Table S6 Related to Figure 4. Hippocampal Volume Predicting the Development of Item-Space Memory.

	Left Hippocampus					Right Hippocampus					· Left and Right Hippocampal Sum				
Effect	**Beta**	**b**	***SE***	***t***	***p***	**Beta**	***b***	***SE***	***t***	***p***	**Beta**	**b**	***SE***	***t***	***p***
(Intercept)	-	0.46	0.026	18	<.0001	-	0.46	0.025	18	<.0001	-	0.46	0.025	18	<.0001
Item-Recognition	0.31	3.5e-1	7.1e-2	4.9	<.0001	0.31	3.5e-1	7.2e-2	4.8	<.0001	0.31	3.4e-1	7.2e-2	4.7	<.0001
Sex [Male]	-0.089	-4.5e-2	3.2e-2	-1.4	0.16	-0.083	-4.2e-2	3.2e-2	-1.3	0.19	-0.08	-4.0e-2	3.2e-2	-1.3	0.21
Start-Volume Head	-0.00091	-1.4e-6	1.0e-4	-0.014	0.99	-0.027	-4.6e-5	1.0e-4	-0.45	0.66	-0.012	-1.1e-5	5.6e-5	-0.2	0.84
Start-Volume Body	-0.097	-1.9e-4	1.2e-4	-1.6	0.12	-0.042	-7.6e-5	1.1e-4	-0.68	0.5	-0.068	-7.2e-5	6.5e-5	-1.1	0.27
Start-Volume Tail	0.0045	1.3e-5	1.8e-4	0.071	0.94	0.039	1.1e-4	1.8e-4	0.61	0.54	0.019	2.9e-5	9.8e-5	0.3	0.76
Start-Age	0.27	6.1e-2	1.7e-2	3.6	0.0004	0.28	6.3e-2	1.7e-2	3.8	0.0003	0.27	6.2e-2	1.7e-2	3.7	0.0003
ΔAge	0.1	2.4e-2	1.3e-2	1.8	0.071	0.12	2.9e-2	1.3e-2	2.2	0.028	0.1	2.4e-2	1.4e-2	1.8	0.078
ΔHead	0.055	2.5e-4	6.1e-4	0.41	0.69	-0.086	-4.2e-4	6.5e-4	-0.65	0.52	0.012	3.6e-5	4.1e-4	0.087	0.93
ΔBody	-0.0065	-3.0e-5	6.5e-4	-0.046	0.96	-0.018	-8.3e-5	6.3e-4	-0.13	0.9	0.0087	2.5e-5	3.9e-4	0.065	0.95
ΔTail	-0.1	-1.2e-3	1.5e-3	-0.78	0.44	-0.14	-1.7e-3	1.7e-3	-0.99	0.32	-0.13	-8.7e-4	9.7e-4	-0.9	0.37
Start-Age x ΔAge	-0.17	-2.7e-2	1.2e-2	-2.2	0.027	-0.21	-3.4e-2	1.2e-2	-2.7	0.0077	-0.20	-3.1e-2	1.3e-2	-2.5	0.014
Start-Age x ΔHead	-0.062	-2.4e-4	5.5e-4	-0.44	0.66	-0.055	-2.3e-4	5.5e-4	-0.42	0.68	0.0019	4.6e-6	3.3e-4	0.014	0.99
Start-Age x ΔBody	-0.2	-9.2e-4	6.7e-4	-1.4	0.17	-0.11	-4.7e-4	5.8e-4	-0.81	0.42	-0.13	-3.7e-4	3.8e-4	-0.97	0.33
Start-Age x ΔTail	0.18	1.9e-3	1.4e-3	1.4	0.16	-0.33	-4.0e-3	1.8e-3	-2.3	0.025	-0.012	-8.2e-5	1.0e-3	-0.078	0.94
ΔAge x ΔHead	-0.035	-7.7e-5	3.2e-4	-0.25	0.81	0.13	3.2e-4	3.6e-4	0.88	0.38	-0.015	-2.2e-5	2.3e-4	-0.096	0.92
ΔAge x ΔBody	0.093	2.1e-4	3.3e-4	0.62	0.54	0.025	5.5e-5	3.2e-4	0.17	0.86	0.06	8.3e-5	1.9e-4	0.43	0.67
ΔAge x ΔTail	0.0033	1.9e-5	8.0e-4	0.024	0.98	0.16	9.6e-4	9.2e-4	1	0.3	0.071	2.5e-4	5.1e-4	0.49	0.63
Start-Age x ΔAge x ΔHead	0.091	1.9e-4	2.9e-4	0.63	0.53	0.12	2.4e-4	3.1e-4	0.78	0.44	0.034	4.2e-5	1.9e-4	0.22	0.82
Start-Age x ΔAge x ΔBody	0.17	3.9e-4	3.5e-4	1.1	0.27	0.2	4.4e-4	3.2e-4	1.4	0.18	0.18	2.5e-4	2.0e-4	1.3	0.21
Start-Age x ΔAge x ΔTail	-0.19	-1.0e-3	7.4e-4	-1.4	0.18	0.41	2.4e-3	9.6e-4	2.5	0.012	0.024	8.3e-5	5.6e-4	0.15	0.88

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.